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The Neurohypophysial Peptides, Learning, and Memory Processing[a]

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It was almost thirty years ago that the first indication of the involvement of neurohypophysial peptides in cognitive processes was reported. It was found that the removal of the posterior pituitary gland, an intervention that disturbed pituitary-adrenal responsiveness to emotional stressors, also impaired the maintenance of an avoidance behavior in the rat. This deficit could be restored by treatment with vasopressin.[1] That vasopressin also normalized impaired avoidance learning behavior of hypophysectomized rats indicated that this effect was not due to the release of adrenocorticotroph hormone or related neuroactive peptides from the anterior pituitary.[2] Vasopressin administration in the intact rat caused a long-term maintenance of active avoidance behavior.[3] The hypothesis was formulated that vasopressin affected long-term memory processes. Finally in the seventies, it became clear that oxytocin, although it frequently mimicked the effects of vasopressin, had intrinsic behavioral activity of an opposite nature, and was regarded as an amnesic neuropeptide. In addition, time-dependent actions of vasopressin and oxytocin suggested that the neuropeptides affected both consolidation and retrieval of memory.[4]

These initial studies were followed by hundreds of reports that were extensively and repeatedly reviewed.[5-7] Although the interpretation of the data was never uniform, it was generally recognized that vasopressin and oxytocin affected cognitive behavior, but certain behavioral actions were not easily reconciled with a mnemonic hypothesis. Despite all the knowledge, the mechanisms by which neurohypophysial hormones exerted long-term effects on behavior were not understood. This notion concerned either network or cellular/molecular levels. For example, it was not specified which one(s) of the multiple vasopressinergic systems were involved in learning and memory,

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and what were the functions of the other circuits. It was well established that vasopressin was expressed in a number of separate circuits in the brain.[8] Although the projections of these neurons presupposed involvement in certain functions, the evidence favored a high degree of complexity. First, the hypothalamo-neurohypophysial neurons seemed to represent the classical neuroendocrine pathway of vasopressin that was involved in peripheral physiological effects of antidiuresis and/or pressor activity. However, dysfunction of the system also resulted in a behavioral deficit that was corrected by peripherally administered vasopressin.[1] Second, the medial amygdala/bed nucleus of the stria terminalis vasopressinergic cell bodies that project to the lateral septum, ventral hippocampus, locus ceruleus, and the habenular area were proposed to be involved in behavioral and physiological thermoregulation,[9,10] convulsive disorders,[11] physiological and behavioral events related to late pregnancy and parturition,[12,13] male sexual behavior,[14] and in cellular and behavioral learning and memory.[15,16] This vasopressinergic system appeared to be sexually dimorphic and regulated by the male gonadal hormone testosterone.[17] Were all these properties represented by the very same neuronal network or did diversity exist within the network? A distinct receptor system for vasopressin and oxytocin[18] seemed to provide a solution for the question. That vasopressin affected neuronal functions via both vasopressin V_{1a} type and oxytocin receptors[6,7] opened the possibility that various functions within a network were mediated by various (sub)types of receptors. Finally, much knowledge was accumulated concerning the molecular mechanisms underlying the neuronal actions of vasopressin and oxytocin,[19] but the molecular basis of long-term effects remained to be elucidated.

In the present paper attention is focused on the contribution of peripheral factors, like catecholamines and gonadal hormones, to the action of vasopressin on learning and memory processes. The role of the central nucleus of the amygdala in these interactions is emphasized. The contribution of central amygdaloid vasopressinergic mechanisms to learning and memory was reinforced by the findings that vasopressin is a powerful modulator of behavioral passivity and concomitant (parasympathetic) physiology, and that this nucleus plays a specific role in coping with conditioned environmental challenges. The final discussion is directed to the heterogeneity of vasopressinergic mechanisms that influence behavior and physiology, including learning and memory. In this context the question is raised as to whether the mnemonic action of vasopressin through hypermnesia contributes to mental pathology.

INTERACTIONS OF ADRENOMEDULLARY HORMONES AND VASOPRESSIN IN MEMORY MODULATION

The interest in investigating the involvement of adrenomedullary hormones in the action of vasopressin on learning and memory was initiated by several findings. First, vasopressin was known to reverse experimentally induced memory loss (amnesia: see Bohus[20]). Second, the influence of certain drugs (e.g. amphetamine) on memory processing appeared to be mediated through adrenomedullary hormones.[21] Third, McGaugh and his colleagues[22] showed the influence of circulating epinephrine on consolidation of memory in intact rats. Postlearning administration of epinephrine enhanced memory at low and moderate doses and impaired it at higher doses. Fourth, adrenalectomy or adrenomedullectomy resulted in amnesia for an aversive experience in male rats.[23] Peripheral administration of low and moderate doses of epinephrine reinstated memory. High doses of epinephrine were ineffective in this respect. Norepinephrine was less effective than epinephrine to normalize memory. But remarkably, the effective range was smaller for norepinephrine—that is, lower doses seemed to be

ineffective. Based on observations in intact and adrenalectomized rats, it was proposed that epinephrine via a β-adrenergic mechanism facilitated memory, whereas norepinephrine via α-adrenergic receptors served as an amnesic hormone. Finally, adrenergic mechanisms in the brain, particularly in the amygdala, were proposed to mediate the effect of peripheral catecholamines on memory.[22] The memory action of vasopressin required an intact noradrenergic transmission in the brain.[15]

Neither postlearning nor preretention administration of vasopressin subcutaneously or intracerebroventricularly reversed the amnesia in adrenalectomized or adrenomedullectomized rats in a passive avoidance task.[24] These findings suggested that a properly functioning adrenal medulla was essential for the mnemonic action of vasopressin. Two alternative hypotheses were developed. First, the release of epinephrine by vasopressin in intact rats might have caused the changes in memory functions. Second, epinephrine might act permissively to allow vasopressin to facilitate memory.

In order to test these hypotheses postlearning and/or preretention administration of vasopressin was combined with a peripheral injection of a low, a submaximally effective moderate, and an ineffective high dose of epinephrine. Vasopressin caused a facilitation of avoidance behavior in epinephrine-pretreated rats provided that the amine was administered shortly before the peptide. Thus, the effect of low and moderate doses of epinephrine (0.00025 to 0.025 μg/kg) were dose-dependently enhanced by vasopressin (1 or 6 μg/rat) in adrenalectomized rats, when the two treatments were given immediately after the single learning trial (FIG. 1). The very same kind of results were obtained with the combination of treatments shortly before the retention test. The slight facilitatory effect of epinephrine at low and moderate doses (0.005 to 0.5 μg/kg) were enhanced by vasopressin in a dose-dependent manner (FIG. 2). Combination of epinephrine administration postlearning and vasopressin injection before the retention test failed to cause more changes in the avoidance behavior than the given dose of amine alone. These results suggested that the presence of circulating epinephrine and probably a momentary occupation of a certain subpopulation of β-adrenergic receptors were essential to influence memory for a long term by vasopressin. Accordingly, the experimental findings favored the second hypothesis—that is, epinephrine caused a permissive action to allow vasopressin to facilitate memory.

The results with the high doses of epinephrine were more complicated. The effects of vasopressin depended on both the dose of the peptide and the dose of epinephrine (FIG. 3). Vasopressin in a dose of 1 μg/rat failed to alter the ceiling effects of epinephrine doses of 0.05 and 0.5 μg/kg, but it substantially facilitated avoidance behavior of rats treated with 5.0 or 50.0 μg/kg epinephrine. The higher dose of vasopressin (6 μg/rat) inhibited the effect of 0.05 μg/kg epinephrine, failed to alter the ceiling effect of 0.5 μg/kg, but facilitated the behavior of rats receiving 5.0 or 50.0 μg/kg epinephrine. In the case of preretention treatment, a slight inhibition was found only at the higher dose of vasopressin (6 μg/rat) in combination with 50.0 μg/kg epinephrine (FIG. 2). Other combinations, for example, 1 μg vasopressin with 50 or 125 μg/kg epinephrine or 6 μg vasopressin with 125 μg/kg epinephrine, appeared to facilitate avoidance behavior. A postlearning high dose of epinephrine and preretention administration of vasopressin were not effective.

The results suggested that vasopressin reversed the amnesic effects of high doses of epinephrine provided that α-adrenergic receptors were probably occupied by the catecholamine. The inhibitory effect of vasopressin was probably related to overarousal as induced by the peptide superimposed on a mixed β- and α-adrenergic effect of epinephrine. The effects of various doses of postlearning vasopressin often showed an inverted U-shaped curve.[25]

The results described here were replicated with adrenomedullectomized instead of adrenalectomized rats, intracerebroventricular instead of peripheral injection of

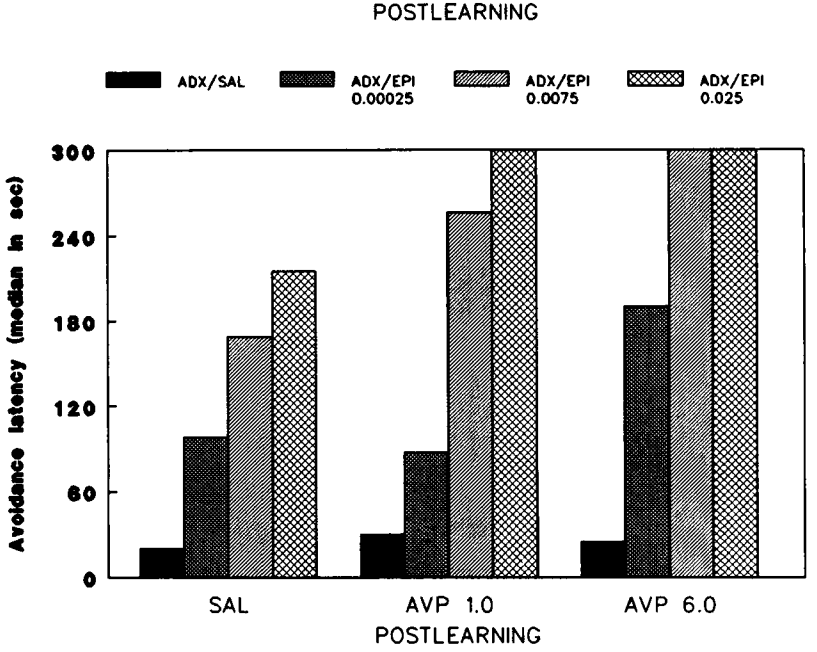

FIGURE 1. The effects of postlearning administration epinephrine (EPI) and/or arginine-vasopressin (AVP) on the retention of a one-trial learning passive-avoidance response in adrenalectomized rats. Latency to reenter the former shock compartment one day after learning was used as the measure of memory. Sham-operated rats scored the maximal latency of 300 sec. The EPI doses were expressed in μg/kg b.w., whereas the AVP dose was expressed in μg/per rat of an average of 250 g body weight. Treatments were given subcutaneously. Seven to eight animals per group.

vasopressin, and with administration of norepinephrine in high doses. Accordingly, the findings were not affected by the presence or absence of circulating corticosterone and by the route of administration of the peptide. Experiments are in progress to determine the nature of β- and α-adrenergic receptors that were involved in the memory-stimulating or inhibitory effects of circulating catecholamines.

EPINEPHRINE, VASOPRESSIN, AND THE AVOIDANCE BEHAVIOR OF BRATTLEBORO RATS

In order to determine whether a cooperative action between vasopressin and epinephrine was of a general validity, the effects of adrenalectomy, vasopressin, and epinephrine treatments were also investigated in male Brattleboro rats homozygous or heterozygous for hereditary hypothalamic diabetes insipidus.[26] Although there was no general consensus about the deficits in learning and memory of these Long-Evans-derived pigmented rats,[27] probably due to both procedural and substrain differences, the male homozygous rats showed serious retention deficits in our hands.[28,29] The deficit was corrected by either postlearning or preretention vasopressin.

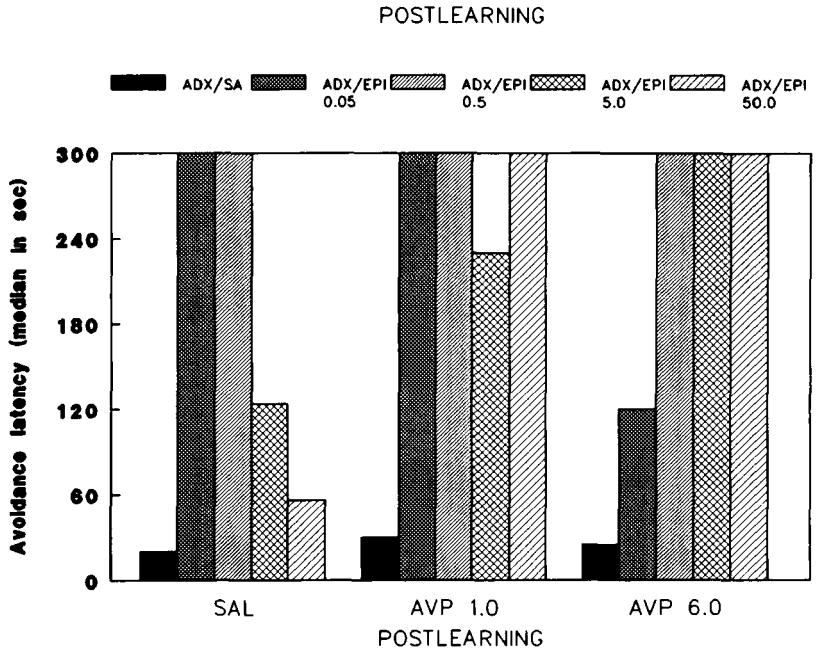

FIGURE 2. The effects of preretention administration of epinephrine and/or arginine-vasopressin on the passive avoidance behavior of adrenalectomized rats. Treatments were given 60 min before the test. *Seven to nine rats per group. For abbreviations and other details see* FIGURE 1.

FIGURE 4 shows that peripheral administration of two doses of vasopressin facilitated avoidance behavior of sham-operated homozygous and heterozygous rats. The same doses of the peptide were not effective in the adrenalectomized Brattleboro rats. In addition, corticosterone substitution did not change the ineffectiveness of vasopressin.

FIGURE 5 shows that an intermediate and a high dose of epinephrine did not facilitate the avoidance behavior of either the sham-operated or the adrenalectomized homozygous diabetes insipidus rats. In the heterozygous line both doses were effective in the sham-operated animals, whereas the intermediate dose was facilitating avoidance behavior in the adrenalectomized rats. The ineffectiveness of the high dose of epinephrine was in agreement with the findings in adrenalectomized Wistar rats. The sensitivity of intact and adrenomedullectomized Wistar rats towards epinephrine was lower than in the adrenalectomized animals.[23] Taken together, the results obtained in Brattleboro rats suggested that the action of peripheral epinephrine on memory processes required vasopressin for cooperative action.

Vasopressin is not the only neuropeptide that affects learning and memory processes.[21] The question was asked whether the mnemonic action of these peptides used the same mechanisms as did vasopressin. Therefore, an ACTH-related peptide, ACTH 4-10, and an endogenous opioid peptide, met-enkephalin, were also administered to adrenalectomized Brattleboro rats homozygous for hereditary diabetes insipidus. It appeared that postlearning administration of both peptides was effective in facilitating

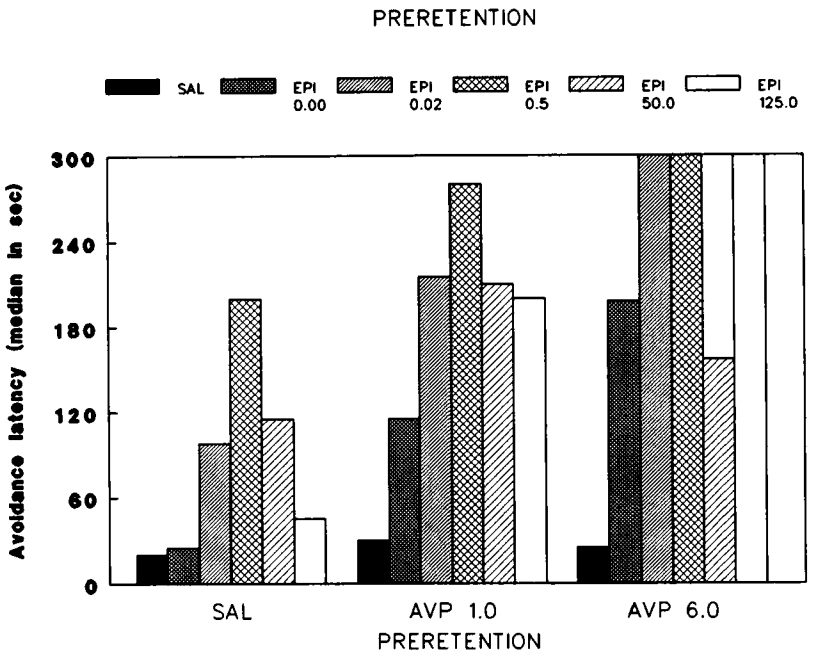

FIGURE 3. The effect of postlearning administration of epinephrine in moderate and high doses and/or of arginine-vasopressin on passive-avoidance retention of adrenalectomized rats. Seven to eight animals per group. For further details, see FIGURE 1.

the avoidance behavior of the Brattleboro rats. These results suggested that ACTH 4-10 and met-enkephalin used a different access to memory processing than vasopressin and epinephrine.

SEX DEPENDENCE OF THE ANTIAMNESIC EFFECT OF VASOPRESSIN

A part of the vasopressinergic innervation in the limbic forebrain of the rat is androgen-dependent. Vasopressin containing fiber density in the lateral septum was higher in males than in females. Castration in the males reduced the density to the levels of females, but testosterone replacement normalized it.[17,30] Testosterone modulated the expression of the vasopressin gene in the neurons of the bed nucleus of the stria terminalis of adult male rats.[31] At the behavioral level vasopressin appeared to mimic androgen effects on male sexual and agonistic behavior following castration.[14,32] The involvement of the androgen-dependent vasopressinergic system in social memory processes in male, but not in female, rats was also suggested.[33-36]

Our approach to investigate sex dependence of the mnemonic effect of vasopressin was based on the robust antiamnesic effects of peripheral or central administration of vasopressin.[19,37] In addition, habituation of open-field exploration was selected as a mnemonic test in order to avoid complications presented by sex differences in conven-

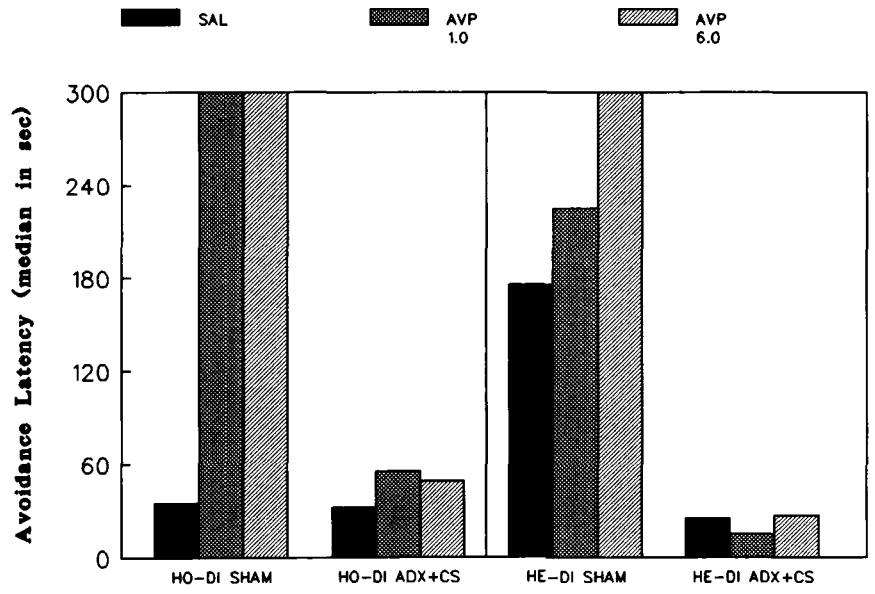

FIGURE 4. Postlearning arginine-vasopressin administration and avoidance behavior of sham-operated (SHAM) or adrenalectomized (ADX) and corticosterone (CS)-supplemented Brattleboro rats either homozygous (HO-DI) or heterozygous (HE-DI) for hereditary hypothalamic diabetes insipidus. Five rats per group. For further details, see FIGURE 1.

tional learning and memory tests. Adult male and female rats explored a novel field rather vigorously at the first exposure. A substantial reduction of exploratory activity upon repeated exposure suggested memory of the environment. Injection of pentylenetetrazol that induced tonic-clonic seizure behavior, immediately after the first exposure, that is postlearning, resulted in a partial amnesia for the explored environment: the rats showed much less reduction in exploratory activity than their controls. The degree of amnesia was more or less the same for both sexes. FIGURE 6 shows that administration of vasopressin before the second test dose-dependently reversed amnesia in the males, whereas the treatment was without significant effect in the females.

These results suggested sex dependence of vasopressin for reversing experimental amnesia. Experiments in progress should present the final evidence that androgen-dependent projection areas from the bed nucleus of stria terminalis were involved. The central amygdala may be a site through which pentylenetetrazol-induced amnesia could be reversed by vasopressin.[37]

INVOLVEMENT OF THE CENTRAL AMYGDALA IN THE MODULATION OF MEMORY BY VASOPRESSIN

Despite the neuroanatomical and functional multiplicity of the brain vasopressinergic systems,[8,15,37] there were a number of reasons to focus our interest on the central amygdaloid nucleus as a probable key structure for mediating a series of effects of vasopressin that are related to learning and memory. First, the central amygdala ap-

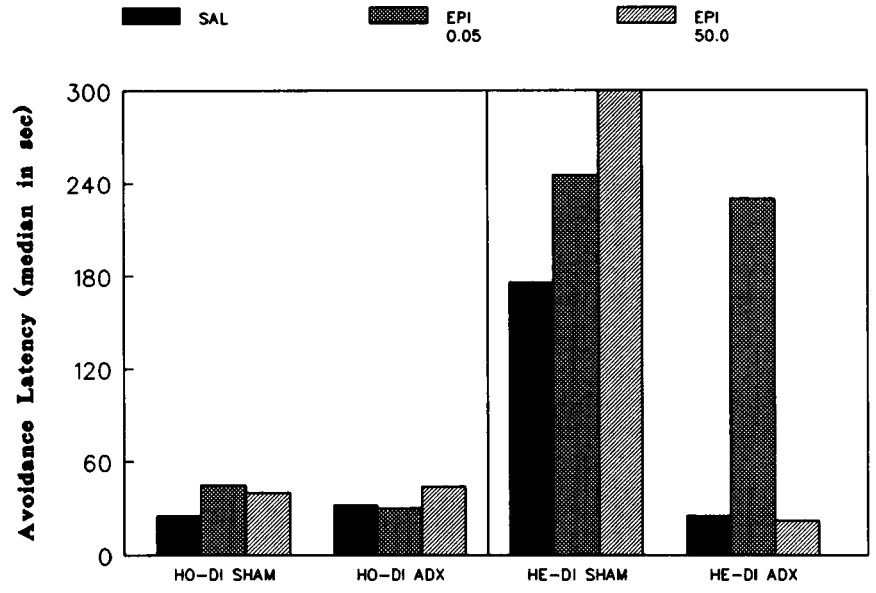

FIGURE 5. Postlearning administration of epinephrine and passive avoidance behavior in Brattleboro rats. For further details see FIGURES 1 and 4.

peared to receive vasopressinergic innervation probably from the bed nucleus of the stria terminalis, whereas oxytocinergic pathways were known to arise from the hypothalamic paraventricular nuclei.[38] It contained a high density of vasopressin and oxytocin receptors.[39-41] Second, the functional heterogeneity of this nucleus from a neurobiological point of view predisposed it as a major integrator of external and internal influences on adaptation, particularly on learning and memory. The central amygdala appeared to play a central role in the initiation-acquisition and consolidation of the environmental information (see Aggleton[42]). According to McGaugh's view, the amygdala served to modulate the storage of information at other brain sites via the activation of physiological systems by affective stimulation.[43] This view implied that the amygdala was the site of generalized modulation of memory storage by hormones and neurotransmitter systems via the activation or inhibition of noradrenergic input to the structure. Interestingly, unimpaired noradrenergic neurotransmission to the limbic forebrain appeared to be essential in facilitating memory by vasopressin.[15] Accordingly, the central amygdala appeared to be a likely candidate of mutual interactions between circulating epinephrine and centrally (or peripherally) available vasopressin.

A low dose of vasopressin (20 pg) infused into the central amygdala of resting rats in their home cage caused a decrease in the heart rate that lasted for at least one hour after termination of the infusion. The resting behavior of the nonstressed rats did not change with this dose of vasopressin.[45] A higher dose of vasopressin (200 pg) and low doses of oxytocin (20 and 200 pg) failed to affect heart rate and behavior. The highest dose of vasopressin and oxytocin (2 ng) elicited a transient acceleration of heart rate with concomitant increase in behavioral activity. These latter effects were blocked by pretreatment with a selective oxytocin antagonist, dPTyr(Me)OVT. All

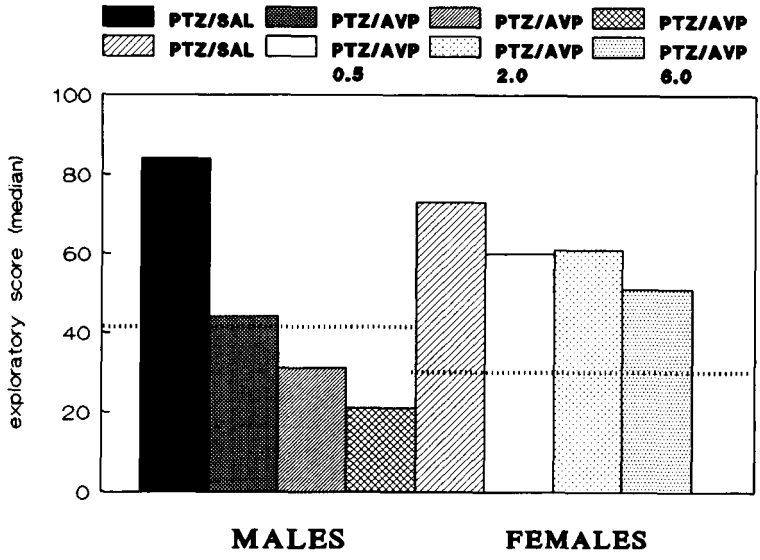

FIGURE 6. Sex dependence of the reversal of pentylenetetrazol (PTZ)-induced amnesia for exploration of a novel environment by arginine-vasopressin in male and female rats. PTZ was administered i.p. immediately after the first exposure to the novel open-field in a dose of 4.5 mg/kg. AVP was administered 60 min before the second exposure to the field. Exploratory scores represent the number of floor units entered on the second day. Broken lines show the behavior of nonamnesic controls (PTZ treatment six hours after the first exposure). Six animals per group.

doses of vasopressin and oxytocin increased the circulating corticosterone levels, but failed to affect plasma catecholamine concentrations.

These results deserved attention from a few different point of view. First, as in a number of conditioned behavioral situations,[7,19] vasopressin and oxytocin exerted an opposite physiological effect probably activating and inhibiting the output to the dorsal motor nucleus via a monosynaptic connection.[46] However, activation of the vagus was probably evoked via vasopressin receptor of V_{1a} type, and the inhibition via the oxytocin receptor in the central amygdala. The elevation of the corticosterone level, that is, activation of the hypothalamo-hypophysial-adrenal system via the paraventricular hypothalamic nuclei[47] by both vasopressin and oxytocin, was elicited via the oxytocin receptor. Facilitation of active and passive avoidance behaviors by vasopressin (and its analogues) appeared to be mediated via the oxytocin receptor in the brain,[7] for which vasopressin was an agonist and oxytocin an inverse agonist. In contrast, it was shown that the action of peripheral vasopressin on various learning and memory tasks was blocked by the vasopressor antagonist dPTTyr(Me)arginine-vasopressin.[6] Accordingly, vasopressin effects on memory processes may be induced via mechanisms that aroused the sympathetic system, but also through mechanisms that caused vagal activation. Indeed, abundant evidence suggested that vasopressin induced behavioral arrest and passivity accompanied by vagal activation and inhibition of sympathetic outflow.[44]

VASOPRESSIN, BEHAVIORAL IMMOBILITY, AND PARASYMPATHETIC ACTIVATION

Vasopressin enhanced the duration of behavioral arrest and immobility in response to the mild stressor of sudden silence superimposed on low-intensity background noise. The peptide also intensified the bradycardiac (vagally controlled) heart rate response that accompanied the behavioral arrest in young adult rats. In addition, the bradycardiac reaction that was absent in aged rats appeared to be restored by vasopressin.[48] Attenuated parasympathetic activation, as observed in aged rats in a one-trial learning conditioned immobility situation, was also restored by vasopressin administration.[44] Amphetamine, but not apomorphine, was also effective in aged rats in both the sudden silence and conditioned immobility tests, suggesting the involvement of noradrenergic rather than dopaminergic mechanisms.[48]

The bradycardiac (vagal) component of conditioned emotional responses were enhanced in a number of other situations where immobility or withdrawal represented the behavioral component.[44] The behavioral and cardiac response was absent under such conditions in Brattleboro rats homozygous for hereditary hypothalamic diabetes insipidus. Administration of vasopressin restored these responses.[49]

Neonatal functioning of the vasopressinergic systems in the brain appeared to have a long-lasting consequence on (im)mobility behavior, and behavioral and autonomic correlates of memory processes. Peripheral administration of vasopressin on postnatal days 3 through 7 in a high (10 μg/kg) and a low (1 μg/kg) dose to male Wistar rats decreased adult immobility, reduced the bradycardiac response during conditioned immobility behavior, and impaired memory processes related to emotional stress. These results were interpreted as the consequence of decreased sensitivity of the vasopressin receptors towards endogenous vasopressin in the adulthood via a neonatal downregulation of receptors.[50] Postnatal vasopressin treatment appeared to downregulate this peptide's receptors in the adult kidney and reduced antidiuretic response.[51,52] Impairment of adult memory by chronic prenatal administration of vasopressin was also observed in the rat.[53]

VASOPRESSIN: A CENTRAL NERVOUS AND PERIPHERAL PEPTIDE OF PASSIVE COPING

Manipulation of the vasopressinergic systems genetically, perinatally, in the adult and aged rats resulted in changes in learning and memory processing as reflected in the behavioral and autonomic parameters. Vasopressin enhances passivity and parasympathetic activation, whereas impairment of vasopressinergic function resulted in more active behavior with memory deficits and sympathetic activation. It became clear that to learn about the environment and to cope using memory allowed more than one expression of adaptation. Animals (mice, rats, monkeys) and men might adopt two kinds of strategies to cope. The active strategy was characterized by rapid learning of active responses (fight or flight) towards the social and nonsocial environment, a high degree of stereotyped behavior and a low degree of immobility and attention. The physiological characteristic was described as a high degree of sympathetic activation. In contrast, the passive strategy was specified as a conservation/withdrawal response pattern with a high degree of immobility and attention, and with a low degree of fight/flight behavior. A high degree of parasympathetic and pituitary-adrenal activation were the physiological attributes of this coping strategy.[44,54]

In neurophysiological and neuroanatomical studies, a brain circuit was constructed, termed as expectancy/anticipatory response pattern circuit, through which vasopressin

might modulate passive ways of coping.[55] The key structures of the circuit were the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the paraventricular and lateral hypothalamic nuclei, the cuneiform, parabrachial nuclei, and nucleus of the tractus solitarius at lower brain level. The circuits could be characterized by long peptidergic neuronal connections between the nuclei. The circuit appeared to have extensive outputs to parasympathetic and sympathetic autonomic, and hypophyseal neuroendocrine systems. In addition, cognitive and motor outputs could also be recognized through cortical and limbic afferents. Vasopressinergic neurons represented an essential part of the circuit. Descending connections to the lower brainstem and spinal autonomic areas might be vasopressinergic (or oxytocinergic).

As far as the memory processes are concerned, action of vasopressin in the central nucleus of the amygdala via vasopressin, and oxytocin receptors may represent the memorial component of the passive coping. The central amygdala was essential at the phase of learning new information, probably by assuring the optimal neuroendocrine and physiological state for consolidation processes. Activation of the sympatho-adrenal and the pituitary-adrenocortical systems appeared to be essential components of this state. If the central amygdala was damaged before learning, the animals were unable to achieve the optimal state.[56]

Findings obtained with rats and mice selected for the use of practically only passive or only active coping strategies via selection for active avoidance behavior or aggressive attack latency,[57,58] opened new avenues for investigating the physiological involvement of vasopressin in passive coping mechanisms. It was found that vasopressin infusion into the central amygdala of Roman low-avoidance rats, which cope passively, potentiated the conditioned emotional bradycardia and immobility. Actively coping Roman high-avoidance rats practically did not change their behavior and heart rate after vasopressin infusion. In addition, it was found that the vasopressinergic fiber system in the lateral septum was more dense and more vasopressin-containing cell bodies in the bed nucleus of the stria terminalis were present in the brain of passively coping long attack latency mice in comparison with the actively coping short attack latency mice. Castration resulted in the disappearance of vasopressin in both lines, suggesting the testosterone dependence of the innervation. Interestingly, a higher number of immunocytochemically labeled vasopressin neurons was found in the suprachiasmatic nuclei, but not in the paraventricular nuclei of the hypothalamus in the brain of mice selected for a low level of nest-building behavior in comparison with mice selected for a high level of nest-building behavior.[57] Further studies on the genetics and the ontogeny of the peptidergic network and of the receptors should contribute to an understanding of the neurobiology of the differences in relation to coping strategy.

CONCLUDING REMARKS

The starting concept of this paper was to collect data that allow an interpretation (or interpretations) of the heterogeneity of the mnemonic action of neurohypophyseal hormones, in particular of vasopressin. A few general aspects of the findings may be taken as major conclusions. First, peripheral hormones played an important role in the action of vasopressin on memory processes. The actions may be permissive by temporary occupation of certain receptor populations (e.g., adrenergic receptors), or of a more long-term nature as in the case of gonadal hormones. While the gonadal hormones undoubtedly acted on the cells at the gene level of the forebrain vasopressinergic system, the site(s) of interaction between catecholamines and vasopressin remain to be specified. It is generally maintained that catecholamines cannot pass the blood-brain barrier.[58] It is likely that the message from the circulating hormones reaches the

amygdala, a major site of action, via adrenergic receptor activation in the periphery and visceral afferents to the brain.[22] That peripheral vasopressin might use visceral afferentation via changes in the blood pressure has repeatedly been suggested.[6] Whatever the mechanism may be, our result showed that the catecholamine-vasopressin interaction did not depend on the peripheral or central availability of the peptide. It is likely that there is mutual cooperation between the mechanisms operating in the two compartments. Peripheral administration of a behaviorally active dose of vasopressin-enhanced adrenal corticosterone output failed to change epinephrine levels, but inhibited resting and novelty-induced elevation of norepinephrine levels. The effects lasted longer than changes in, for example, blood pressure. The inhibition of sympathetic outflow by the peptide may be a mechanism by which an α-adrenoceptor-induced amnesia is attenuated. Furthermore, sympathetic inhibition may contribute to the parasympathetic outflow as induced by genuine central nervous vasopressinergic activation at the level of the central amygdala or brainstem nuclei.[59]

The parasympathetic component represented an essential chain of the events in the passive way of coping and its relation to memory processes. Evidence suggested that inhibition of the vagal heart response by the peripherally acting methylatropine also attenuates immobility behavior accompanying the conditioned emotional response. More data are becoming available indicating that vasopressin enhances expression of behavioral elements like selective attention, preferential processing of dominant information,[61] and so forth, that are components of passive coping strategy.[4,8,54] The relation of these effects to memory processes is, however, not always clear. More importantly, recent findings showed that vasopressin was essential for conditioned immobility.[62]

One may, however, raise the question how the hypothesis that vasopressin primarily serves those mnemonic processes that belong to the category of passive coping can be reconciled with findings like long-term maintenance of active avoidance behavior in the absence of punishment. This kind of hyperamnesic effect may be synonymous with compulsive behavior. Similarly, disrupting ongoing behavior often reported in appetitive situations (e.g. see Alliot[63]) or induction of taste or place aversion by vasopressin is a reflection of phobic states. If this argumentation is true, the use of vasopressin in different models may serve to study either physiological or pathological processes.

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